Rejections Under 35 USC § 101

The Examiner has rejected claims 1-20, arguing that the claims are not supported by a credible asserted utility or a well-established utility. In response, claims 1 has been deleted and replaced by new claims 21 and 22. New claim 21 is directed to the "treatment" of the listed disorders, and new claim 22 is directed to the "prevention or treatment" of the "pathophysiological manifestations" of the recited diseases. Claims 2, 3, 9 and 15 have been amended and new claims 23, 24 and 25 have been added for consistency with new claim 22 and claims 2, 3 and 4. New claim 26 has been added. Support for the term "preventing" / "prevention" may be found at, for example, pages 5 (line 10), 8 (line 7) and 16 (line 2), and for the expression "pathophysiological manifestations", on pages 5 (lines 13-14) and 16 (lines 2-3), and for the term "airway obstruction" on page 3 (lines 8-10) and page 16 (lines 19-22). In light of the above, reconsideration is respectfully requested.

Rejections Under 35 USC § 112

The Examiner has rejected claims 1-20 pursuant to 35 U.S.C. 112 based on the current scope of the claims which include homologs, analogs, fragments and derivatives of CGRP. In the interest of advancing prosecution, new claims 21 and 22, which replace former claim 1, recite only the species CGRP, adrenomedullin and [Cys(ACM)^{2,7}]CGRP. Applicant reserves the right to pursue any subject matter removed by this amendment in one or more continuation applications.

The Examiner has further rejected claims 1-20 pursuant to 35 U.S.C. 112 based on her interpretation of former claim 1. In response, the applicant respectfully submits that the Examiner has misunderstood the intended meaning of claim 1, in that the features noted by the Examiner are not merely characteristics used to define asthma, but rather, are other disorders which also may be prevented or treated using the method of the invention. These other disorders may, but do not necessarily, coincide with asthma, depending on the situation. Therefore, new claims 21 and 22, which replace former claim 1, have a modified structure to clearly recite this intended meaning.

Rejections Under 35 USC § 102

The Examiner has rejected claims 1-20 as anticipated in light of United States Patent No. 5,858,978 as evidenced by *The Merck Manual*. In response, the applicant respectfully submits the following.

First, the applicant notes that the invention of the instant application was realized prior to the filing date of the '978 Patent, i.e. prior to April 14, 1997. The instant inventor possesses evidence, such as experimental results obtained prior to this date, in support of this assertion. Such evidence can be provided in the form of a declaration upon the Examiner's request.

Second, the applicant respectfully submits that the '978 Patent is not enabling with regard to the use of CGRP for the treatment of asthma and other airway disorders and thus does not teach the use of CGRP for this

purpose. The results presented in the '978 Patent may be summarized as follows.

1. CGRP inhibits the release of IL-1 from macrophages and "giant cells" (multinucleated cells formed by fusion of macrophages);

2. The inhibition noted in (1) is mediated by a cAMP dependent mechanism;

3. CGRP has no effect on IL-6 release from the cell types noted in (1).

Since the immune response involves, among other things, the release of IL-1 by immune cells, the '978 Patent concludes and claims that CGRP may be used to down regulate the immune response via the inhibition of IL-1 release. The '978 Patent mentions in general terms that a relationship exists between cytokine activity and inflammatory reactions, with a particular emphasis on those present in rheumatoid arthritis (see col. 4, lines 12-28). However, it should be noted that the '978 Patent demonstrates a relationship between CGRP and IL-1 release, and that any further extrapolation linking CGRP with lung inflammatory reactions is mere conjecture and is not suggested by the '978 Patent.

Further, it is noted in the '978 Patent that "cytokines are very potent with diverse biological activities which affect nearly every organ when administered *in vivo*" (col. 4, lines 11-14). Such statement leads to the further unfounded prediction that CGRP may be used to treat a number of disorders, listed exhaustively in, for example, column 13 (lines 1-35). Such predicted,

yet unfounded, uses for CGRP are as far reaching as to predict its use as an oral contraceptive (col. 13, line 30). Among the long list of such unfounded predicted applications, as the Examiner has noted, is the treatment of asthma, simply because this disorder involves inflammation. However, the applicant respectfully submits that mere demonstration of inhibition of IL-1 release by macrophages is not equivalent to demonstrating a use of CGRP in the treatment of asthma. The points noted above are also reflected in the claims granted in the '978 Patent, which only cover immunosuppression accomplished by the inhibition of IL-1 and IL-2 release.

Further, the applicant respectfully submits that the accumulation of giant cells during inflammation, which is the focus of the studies presented in the '978 Patent is a distinct feature, unique to the chronic inflammation associated with diseased synovial tissue such as that encountered in rheumatoid arthritis [1]. This point is reflected in the comments relating to the treatment of rheumatoid arthritis in the '978 Patent (col. 12, lines 58-63). In contrast, inflammation linked to asthma is <u>not</u> characterized by an accumulation of giant cells [2] and the mediators responsible for chronic inflammation in the joints <u>are not</u> the same as those associated with asthma [3].

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[1] see Wilkinson, L.S., et al. (1993) *Annals of Rheumatic Diseases* 52:182-184; Weinberg, J.B., et al. (1993) *Immunol. Invest.* 22(5): 365-374.

[2] see Chambers, T.J. (1978) *J. Pathol.* 126(3): 125-148; Sedgewick, J.B. et al. (1994) Eosinophils in asthma, in *Eosinophils in Allergy and Inflammation*, Gleich, G.J. and Kay, A.B. (Eds), 443-454; Bousquet, J., et al. (1990) *New Engl. J. Med.* 323:1033-1039.

[3] regarding arthritis, see Berner, B., etal. (2000) *J. Rheumatol.* 27(5): 1128-1135; Schiff, M.H., et al. (2000) *Ann. Rheum. Dis.* 59 Suppl 1:I103-I108; Lorenz, H.M. (2000) *Expert Opin. Investig. Drugs* 9(7):1499-1510; regarding asthma, see Djukanovic R. (2000) Pathology of asthma, in *New and Exploratory Therapeutic agents for Asthma*, Yeadon, M. and Diamant Z. (Eds), 57-84; Boonstra, A. and Savelkoul, H.F.J. (2000), Activity of T-cell subsets in allergenic asthma, *Ibid.*, 343-360; Holgate S.T. and Busse, W.W. (Eds) Inflammatory Mechanisms in Asthma (1998).

These issues are discussed in the just-noted references and may be summarized as follows:

A) Inflammatory reaction in both rheumatoid arthritis and asthma is under the control of specific and different subsets of T helper lymphocytes (Th cells) which are activated once the antigen/antibody reaction is initiated.

B) The antigen-presenting cells in rheumatoid arthritis are mainly macrophages while those in asthma are mostly dendritic cells.

C) The immune system is able to distinguish between particular types of antigenic challenges and consequently lead to different pathological manifestations.

D) Rheumatoid arthritis is generally considered a disease driven by Th1 cells (IL-1, IL-2, TNF alpha, etc.).

E) Pictures that emerge from studies realized on these diseases are that both Th1 and Th2 cells produce distinct and restricted patterns of cytokines that cross regulate each other, and that induce different manifestations of immune responses.

It is interesting to note that allergen immunotherapy for rheumatoid arthritis is based upon its ability to change a Th1 to a Th2 response by inhibiting IL-1 and TNF alpha production, while that for asthma is based upon

its ability to change a Th2 to a Th1 response by inhibiting IL-4 and/or stimulating IFN gamma production. Therefore, what appears to be beneficial in one case is of no utility in the other.

Further, the applicant notes that asthmatic crisis may be initiated by many factors other than via the triggering of the immune response by a foreign agent, such as cold air, physical exertion and stress (instant application, page 3, line 5).

In conclusion, the applicant respectfully submits that the mere demonstration of the inhibition of IL-1 (and indirectly, IL-2) release from macrophages and giant cells, by CGRP treatment, cannot be extrapolated to the treatment or regulation of any condition involving inflammation, such as asthma, given the pleiotropic nature of cytokine activity, and the enormous variation and complexity of the mediating factors and regulatory systems involved in the manifestation of such disorders.

In contrast to the studies of the '978 Patent, the instant application was the first to demonstrate that CGRP is a strong bronchoprotecting agent. It blocks both early and late phase responses associated with an asthma attack, including the phenomenon of bronchial hyperreactivity (exacerbation). Therefore, the instant application establishes a direct utility for the use of CGRP in the treatment of asthma and related disorders.

Therefore, in light of the above, the applicant respectfully requests reconsideration and that the rejection based on alleged anticipation be withdrawn.

Rejections Under 35 USC § 103

The Examiner has rejected claims 1-20 as obvious in light of the '978 Patent discussed above in view of United States Patent No. 5,510,339. In response, the applicant respectfully submits the following.

The Examiner is respectfully referred to MPEP 706.02(j), second paragraph, which reads in part as follows:

> "To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and **not based on applicant's disclosure**." *(emphasis added)*

As noted above, the '978 patent appears to disclose the following:

1. CGRP inhibits the release of IL-1 from macrophages and "giant cells" (multinucleated cells formed by fusion of macrophages);

2. The inhibition noted in (1) is mediated by a cAMP-dependent mechanism;

3. CGRP has no effect on IL-6 release from the cell types noted in (1).

The '339 patent appears to disclose the following:

1. Topical anesthetics may inhibit eosinophil viability *in vitro*.

2. Some effects on the inhibition noted in (1) may be seen by concomitant treatment with IL-5, which varies depending on IL-5 concentration.

3. Lidocaine treatment of patients suffering from asthma provides some relief of asthma symptoms, and enables a gradual reduction in glucocorticoid dosage.

4. Via references to various prior art it is mentioned that an association exists between eosinophil accumulation and asthma.

Further to the extensive discussion of the '978 patent above, the applicant reiterates that the '978 patent merely teaches CGRP inhibition of IL-1 release via a cAMP-dependent mechanism, and does not teach any

relationship between CGRP and asthma. The '339 patent teaches an effect of topical anesthetics on eosinophil viability *in vitro*, further possibly implicating IL-5, and an effect of lidocaine on the treatment of asthma symptoms *in vivo*. Thus, the only link between these two references is the mention of asthma, which, as noted above, is completely unsupported in the '978 patent. Thus, the applicant first submits that no motivation is present to combine these two references.

Further, the '978 patent attempted and failed to demonstrate an effect of CGRP on IL-6 release, indicating that based on the variation in the activity of different cytokines, there is no justification to assume that different cytokines are involved in the same processes without experimental evidence to that effect. Therefore, an effect on IL-1/IL-2 release ('978 patent) may not be extrapolated into a process thought to involve IL-5 ('339 patent). Therefore, when the scientific data is analyzed, there is not a reasonable expectation of success in combining these references in this regard.

Further, the applicant respectfully submits that it appears that once the Examiner identified the '978 patent, she noted that the present application discussed eosinophil accumulation while the '978 patent did not, and as a result searched for any prior art linking eosinophil accumulation and asthma, thereby identifying the '339 patent. Therefore, it is the view of the applicant that the motivation for the Examiner to combine these two patents was not derived from the prior art, but rather, was gleaned from the instant application,

contrary to the last point among the criteria stated above for making a *prima facie* case of obviousness.

In light of the above, the applicant respectfully requests reconsideration and that all rejections be withdrawn.

It is believed this responds to all of the Examiner's concerns, however if the Examiner has any further questions, she is invited to contact Joy Morrow at 613-232-2486.

Respectfully submitted,

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